REMARKS

Claims 13-16, 18-20 and 27-35 presently appear in this case. Claims 18-20 and 27-29 have been withdrawn from consideration. Claim 14 has been objected to but has been indicated to be allowable if rewritten in independent form. Claims 13, 15 and 16 have been rejected. The official action of December 3, 2004, has now been carefully studied. Reconsideration and allowance are hereby respectfully urged.

Briefly, the present invention relates to an isolated polypeptide which is capable of binding to RIP, which protein is a RIP-associated protein (RAP) encoded by a DNA sequence in a clone deposited in a depository, a fragment thereof which binds to RIP, an analog thereof having no more than 10 changes in the amino acid sequence of RAP, each said change being a substitution, deletion or insertion of an amino acid, which analog binds to RIP, or a derivative thereof by modification of a functional group which occurs as a side chain or a terminal group without changing one amino acid to another.

The examiner states that claims 18-20 and 27-29 stand withdrawn from further consideration as being drawn to non-elected inventions. Please take note that applicants' grounds of traversal remain and applicants retain the right to

file a petition to the Commissioner under 37 C.F.R. §1.144 at an appropriate time.

Claims 13, 15 and 16 have been rejected under 35 U.S.C. §112, first paragraph, as the specification does not reasonably provide enablement for polypeptides that "comprise" any fragment of RAP or for analogs having no more than ten additions or deletions in the amino acid sequence, or derivatives of such analogs. The examiner states that there is insufficient guidance as to which ten amino acids can be changed and still retain binding to RIP. This rejection is respectfully traversed.

First of all, it should be noted that new claim 30 is being submitted which is intended to be drawn only to those embodiments to which the examiner admits to be enabling in the first part of the rejection. It specifies that the polypeptide "consists of" the sequences of (a), (b) or (c). Reference to analogs is omitted. Accordingly, it is urged that the examiner consider claim 30 in its own right and indicate that it is free of this rejection. Similarly, claim 35 is the same as claim 30, but specifies that the amino acid changes are only substitutions and not additions or deletions. As the rejection seems to stress only the additions and deletions, it was thought that the examiner would not object to a claim that only required substitutions. Furthermore, in

order to further remove the new claim from the rejection, the number of changes was diminished from ten to five, as is supported on line 2 of page 40 of the present specification. Accordingly, it is urged that claim 35 also be considered in its own right and indicated to be free of this rejection.

The examiner objects to the language that the polypeptide "comprises" a fragment of (a) which binds to RIP. It should be noted that, regardless of the presence of amino acids upstream and downstream of the fragment, the claim requires that the fragment itself be capable of binding to RIP. Once it is clear that the fragment retains the ability to RIP, there is no reason to believe that addition of residues upstream and downstream thereof will prevent the full polypeptide from binding. In other words, for the most part, the identity of any such additional polypeptides is irrelevant. However, the preamble requires that the entire polypeptide also be capable of binding to RIP. Accordingly, any polypeptide with residues that interfere with the ability of the fragment to bind to RIP, so that the entire polypeptide no longer binds to RIP, is not covered by the claim in any event. The examiner agrees that the fragments *per se* are based on an enabling disclosure. The fact that the claims are broad enough to read on additional residues upstream and downstream thereof should not remove the claim from enablement

in view of the fact that the identity of such residues is largely irrelevant and to the extent that anything is added that prevents the binding ability, it is not covered by the claim anyway. Accordingly, reconsideration and withdrawal of this part of the rejection are respectfully urged.

With respect to analogs, it should be noted that MPEP §2164.01 provides that the question is whether the experimentation needed to practice the invention is undue or unreasonable. If the invention can be practiced without undue or unreasonable experimentation, the enablement requirement is considered to be met.

The amount of experimentation that may be permitted in order to satisfy the enablement requirement of 35 U.S.C. §112 is discussed in *In re Wands*, 858 F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988). See also MPEP §2164.01(a). In this regard, *Wands* states, 858 F.2d at 736-737, 8 USPQ2d at 1404:

> Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. "The key word is 'undue,' not 'experimentation.'"
>
> The determination of what constitutes undue experimentation in a given case requires the application of a standard of reasonableness, having due regard for the nature of the invention and the state of the art. Ansul Co. v. Uniroyal, Inc. [448 F.2d 872, 878-879; 169 USPQ 759, 762-763 (2d Cir. 1971), *cert. denied*, 404 U.S. 1018, 30 L. Ed. 2d 666,

> 92 S. Ct 680 (1972)]. The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed***. [Footnotes omitted - the latter quote being from *In re Jackson*, 217 USPQ 804, 807 (Bd. App. 1982)]

Wands goes on to state, 858 F.2d at 737, 8 USPQ2d at 1404:

> Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in *Ex parte Forman* [230 USPQ 546, 547 (Bd. Pat. App. & Int. 1986)]. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. [Footnotes omitted]

In analyzing these factors in this case, the conclusion must be reached that the experimentation is not undue.

With respect to the breadth of the claims, claim 13, in part (a), is directed to a specific polypeptide, which the examiner concedes is sufficiently enabled (see the allowability of claim 14). Part (c) includes analogs thereof having no more than ten substitutions, deletions or additions of amino acid residues, with each such change being a substitution, deletion or insertion of a single amino acid.

It further specifies that the analog must bind to RIP. It should be noted that the amino acid sequence of SEQ ID NO:2 has 522 residues. Thus, ten changes in the 522 residue sequence amounts to only about 1.9%, i.e., the claimed analogs have a minimum of greater than 98% identity to the specified sequence.

While claim 13(c) is somewhat broader than the specific sequence of (a), the claimed scope is necessary in order to reasonably cover the invention. In MPEP §2164.08, relating to enablement commensurate in scope with the claims, the MPEP quotes the following from *In re Goffe*, 191 USPQ 429, 431 (CCPA 1976):

> [T]o provide effective incentives, claims must adequately protect inventors. To demand that the first to disclose shall limit his claims to what he has found will work or to materials which meet the guidelines specified for "preferred" materials in a process such as the one herein involved would not serve the constitutional purpose of promoting progress in the useful arts.

It should be noted that the definitions of fragment, analog and derivative at claim 13(b), (c) and (d), respectively, all require that the polypeptide have the ability to bind to RIP. The polypeptides have utility merely by binding, for example in affinity chromatography, and, therefore, it is not absolutely necessary to assay for intracellular activity. In view of the stated activity and

the direction in the specification, which will be discussed below, and the reasonable breadth of the analogs, the breadth is not unduly broad and the experimentation to find everything within the scope of these claims would not be undue.

The nature of the present invention is such that substantial experimentation is reasonably conducted by those of ordinary skill in the art. The present claims are directed to recombinantly-produced polypeptides. Applicants concede that there is not 100% predictability in this field. However, this does not mean that an applicant must be limited to exemplified embodiments. As long as it is shown that the experimentation to determine what falls within the claim is not undue, the enablement requirement is met. As discussed below, the experimentation is not undue.

As to the state of the prior art, there is no close prior art. Thus, there is no prior art reason for limiting the scope of the claims. Furthermore, a review of prior patents will show that it is common for those of ordinary skill in the art to take part in this degree of experimentation as there are scores of patents that include claims with novel proteins and analogs thereof with 95% or even less identity. This is not a case of first impression.

As to the level of one of ordinary skill, inventions involving biotechnology involve a very high level of ordinary

skill. Because of this extremely high level of ordinary skill, even complex experimentation is not necessarily undue or unreasonable.

The next two *Wands* factors, the level of the predictability in the art and the amount of direction provided by the inventor, go hand in hand. As to the predictability in the art, when changing the sequence by less than 2%, there would be an expectation that the function is maintained. Thus, it is reasonably predictable that such a small number of random changes will work, but in any event, it is readily testable in order to determine which will have the claimed function and which will not have the claimed function. The present claim always requires that the result of the amino acid changes have the ability to bind to RIP, i.e., by definition, the activity must be retained. The present specification states in paragraph 89:

> While any technique can be used to find potentially biologically active proteins which substantially correspond to RAP proteins, one such technique is the use of conventional mutagenesis techniques on the DNA encoding the protein, resulting in a few modifications. The proteins expressed by such clones can then be screened for their ability to bind to various RIP and to modulate RIP activity in modulation/mediation activity of the intracellular pathways noted above.

See also paragraph 97, where it states:

> When the exact effect of the substitution or deletion is to be confirmed, one skilled in the art will appreciate that the effect of

> the substitution(s), deletion(s), etc., will be evaluated by routine binding and cell death assays. Screening using such a standard test does not involve undue experimentation.

Furthermore, substantial guidance is provided in the present specification as to preferred substitutions which would be expected to retain the activity of the base compounds, i.e., the RAP protein. Note, for example, paragraphs 90-97. Those of ordinary skill in the art are aware that binding assays are relatively simple tests. Whole libraries can be screened at one time with the yeast two-hybrid assay described in the Example beginning at paragraph 170 of the present specification. Other binding assays using microarray technology are well known in the art and can test thousands of compounds at once for binding. This is not undue experimentation in this art, particularly in view of the small number of amino acids that may be changed in accordance with the language of the claims. Accordingly, it is apparent that there is substantial direction provided in the specification about how to do these standard binding assays. This is all that is necessary to do in order to determine whether any given analog having no more than ten amino acid changes has the ability to bind RIP. These minor changes are not unreasonable. Accordingly, substantial direction is provided by the specification.

As far as working examples are concerned, as discussed above, a working example of the yeast two-hybrid binding assay is given in the specification. While there are no working examples given in the specification for analogs, fragments and derivatives, the guidance of the specification explains how to determine whether any given compound falls within the scope of the claims, and therefore additional working examples are not necessary.

Finally, the last *Wands* factor is the quantity of experimentation needed to make or use the invention based on the content of the disclosure. It is true that substantial experimentation will be necessary. However, as stated at MPEP §2164.06, the test is not merely quantitative since a considerable amount of experimentation is permissible if it is merely routine or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed. Time and expense are not the controlling factors. Procedures for making variants of the RAP protein which have at least 98% identity with the sequence thereof are conventional in the art, such as the technique detailed in paragraphs 99-106 of the present specification.

The assays involved to determine whether any such analog has the ability to bind RIP are routine, as is

disclosed in the specification and discussed above. All of the claimed analogs must possess the specified activity of being able to bind RIP. There is a reduction to practice of the disclosed species of RAP protein. The fact that any single amino acid change might have a profound effect or no effect, is not really dispositive. Here, standard binding assays are known and so any given analog can readily be tested without undue experimentation. Indeed, whole libraries of analogs can be tested simultaneously. Thus, applicants need not rely upon predictability of analogs with respect to changes (even though there is reasonable predictability with analogs of greater than 98% identity), but are relying on testing in the standard assays described in the specification and discussed above, which can be carried out in large numbers at the same time.

The level of skill in the art is high and the assays are standard and can be conducted with many different analog sequences at the same time. Thus, while substantial experimentation may be needed to establish all of the sequences of which fall within the scope of the claim, i.e., meet the functional requirement of binding to RIP, such experimentation is not undue or unreasonable. For any given sequence, the testing is virtually negligible in order to test for binding to RIP. Indeed, the *Wands* case itself found that

routine screening does not necessarily amount to undue experimentation.

Accordingly, as in *In re Wands*, analysis of the facts of the present case, considering the factors enumerated in *Ex Parte Forman*, leads to the conclusion that undue experimentation would not be required to practice the invention. There was a high level of skill in the art at the time when the application was filed, and all of the methods needed to practice the invention were well known. Accordingly, reconsideration and withdrawal of this part of this rejection are respectfully urged.

It should be noted that new claim 31 limits the analog paragraph of claim 13 so as to have no more than five changes. New claim 32 limits the analog paragraph of claim 13 so as to have no more than three changes. Both of these are supported by paragraph 89 on page 40 of the present specification. New claim 33 specifies that there is only one change in the amino acid sequence, as is supported by paragraph 88 on page 39 of the specification. It is requested that the examiner consider these claims independently for satisfaction of the enablement requirement as the number of changes become diminishingly smaller. Certainly some degree of breadth in claiming a novel protein is permissible.

Claims 13, 15 and 16 have been rejected under 35 U.S.C. §112, first paragraph, as containing subject matter that was not described in the specification in such a way as to reasonably convey to one in the relevant art that the inventors had possession of the claimed invention. This rejection is respectfully traversed.

As pointed out above, SEQ ID NO:2, which is encoded by the DNA of the deposited clone of claim 13(a), has 522 residues. The claims do not encompass more than ten amino changes therein, which amounts to only about 1.9%. Accordingly, the claimed analogs have a minimum of greater than 98% identity to the specified sequence.

The examiner's attention is respectfully drawn to the Revised Interim Written Description Guidelines Training Materials and, particularly, Example 14: "Product-by-Function". In that example, the specification exemplified a protein isolated from liver that catalyzed the reaction of A→B, which isolated protein was sequenced and was determined to have the sequence as set forth in SEQ ID NO:3. The specification also contemplated, but did not exemplify, variants of the protein wherein the variant can have any or all of the following: substitutions, deletions, insertions, and additions. The specification indicated that procedures for making proteins with substitutions, deletions,

insertions, and additions is routine in the art and provided an assay for detecting the catalytic activity of the protein.

This description in the specification is very similar to the description which appears in the present specification. The present specification exemplifies a RAP protein that binds RIP. The sequence of this protein is specified. The specification contemplates, but does not exemplify, variants of the protein wherein the variant can have substitutions, deletions, insertions, and additions. The present specification also indicates that procedures for making proteins with substitutions, deletions, insertions, and additions are routine in the art (see, for example, paragraphs 99-106) and provides an assay for determining whether any given protein binds to RIP. See also paragraph 97.

In Example 14 of the Training Materials, the claim is directed to:

> A protein having SEQ ID NO:3 and variants thereof that are at least 95% identical to SEQ ID NO:3 and catalyze the reaction of A→B.

The present claim 13 is drawn to a method of use that includes an analog of RAP having effectively at least 98% identity with the sequence of RAP and has the ability to bind to RIP. Thus, this claim is substantially identical in format to that of Example 14.

The analysis in the Training Materials acknowledges that procedures for making variants of SEQ ID NO:3 are conventional in the art and that an assay is described which will identify other

proteins having the claimed functionality. Moreover, procedures for making variants of SEQ ID NO:3 which have 95% identity to SEQ ID NO:3 and retain its activity were conceded as being conventional in the art. It would, of course, be understood that procedures for making variants of the polypeptide of paragraph (a) of claim 13, which have 98% identity to that sequence and retain its binding activity to RIP are also conventional in the art.

The analysis goes on to point out that all variants of the claim must possess the specified catalytic activity and must have at least 95% identity to the SEQ ID NO:3. Furthermore, because of the "having" language, the protein claimed may be larger than SEQ ID NO:3 or its variant with 95% identity to SEQ ID NO:3. The analysis points out that the specification contains a reduction to practice of the single disclosed species. The analysis concludes:

> The specification indicates that the genus of proteins that must be variants of SEQ ID NO:3 does not have substantial variations since all the variants must possess the specified catalytic activity and must have at least 95% identity to the reference sequence, SEQ ID NO:3. The single species disclosed is representative of the genus because all members have at least 95% structural identity with the reference compound and because of the presence of an assay which applicant provided for identifying all of the at least 95% identical variants of SEQ ID NO:3 which are capable of the specified catalytic activity. One of skill in the art would conclude that applicant was in possession of the necessary common attributes possessed by the members of the genus.

> Conclusion: The disclosure meets the requirements of 35 USC §112, first paragraph, as providing adequate written description for the claimed invention.

Thus, it is apparent that if the single species disclosed is representative of the genus and an assay is present for identifying the members of the variants that are capable of the specified functionality, the written description requirement is met, regardless of the protein chemistry arguments made by the examiner. Here, the 98% identity is much higher than the 95% identity that was found to satisfy the written description guidelines in the training materials.

As to the examiner's comment that the claim language is open-ended, it is noted that the claim language in Example 14 of the training materials discussed above is also open-ended and was found to be acceptable. In this regard, see also paragraph 111 of the present specification.

Accordingly, with respect to the Guidelines to which the examiner refers, the implementing Training Materials clearly indicate that the present claims satisfy the written description requirement. Reconsideration and withdrawal of this rejection are therefore respectfully urged.

The examiner has objected to claim 14 as being dependent upon a rejected base claim but states that the claim would be allowable if rewritten in independent form. As it is believed that claim 13 is now in condition for allowance,

claim 14 has not yet been written into independent claim form. However, the examiner's indication of its allowability is gratefully acknowledged.

It is submitted that all of the claims now present in the case clearly define over the references of record and fully comply with 35 U.S.C. §112. Reconsideration and allowance are therefore earnestly solicited.

Respectfully submitted,

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